

Proficiency Testing:

Across Borders & Disciplines

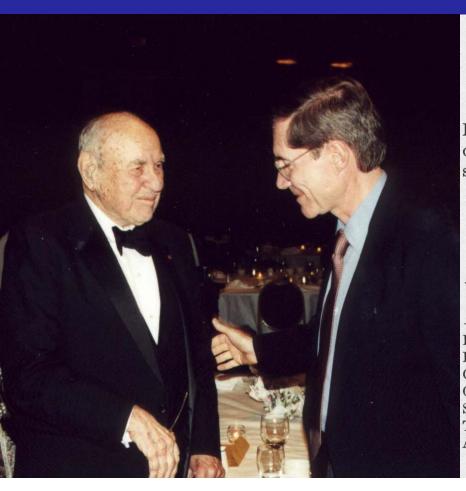
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William F. Sunderman, Jr.

(23 October 1898 -)



A SURVEY OF THE ACCURACY OF CHEMICAL ANALYSES IN CLINICAL LABORATORIES*

WILLIAM P. BELK, M.D., † AND F. WILLIAM SUNDERMAN, M.D. †

In 1946 the Committee on Laboratories of the Medical Society of the State of Pennsylvania proposed a survey‡ to check the accuracy of some of the more common chemical measurements made in hospital laboratories throughout the state. It undertook to do this by distributing solutions which had been carefully

TABLE 1

Number of Determinations Classed as Satisfactory, Unsatisfactory and Gross Error

September Analyses

SUBSTANCE TESTED	SATISFACTORY LIMITS OF RESULTS PER 100 ML.	NUMBER SATISFACTORY	NUMBER UN- SATISFACTORY**	GROSS ERROR**
Hemoglobin	$9.8 \pm 0.3 \mathrm{gm}$.	17	34	11
Hemoglobin	$15.1 \pm 0.5 \mathrm{gm}$.	21	31	3
Glucose	60 ± 10 mg.	33	19	5
Glucose	375 ± 30 mg.	27	24	4
Sodium chloride	456 ± 50 mg.	30	14	2
Total protein	$6.6 \pm 0.4 \text{ gm}.$	18	29	7
Albumin		9	35	7

October Analyses

Many facets of Proficiency Testing

Traceability

Legal Authority

Education

Snapshot of Performance

Measurement Uncertainty

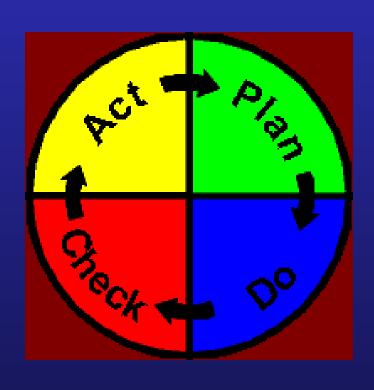
National Infrastructure

Accreditation

International Measurement Structure

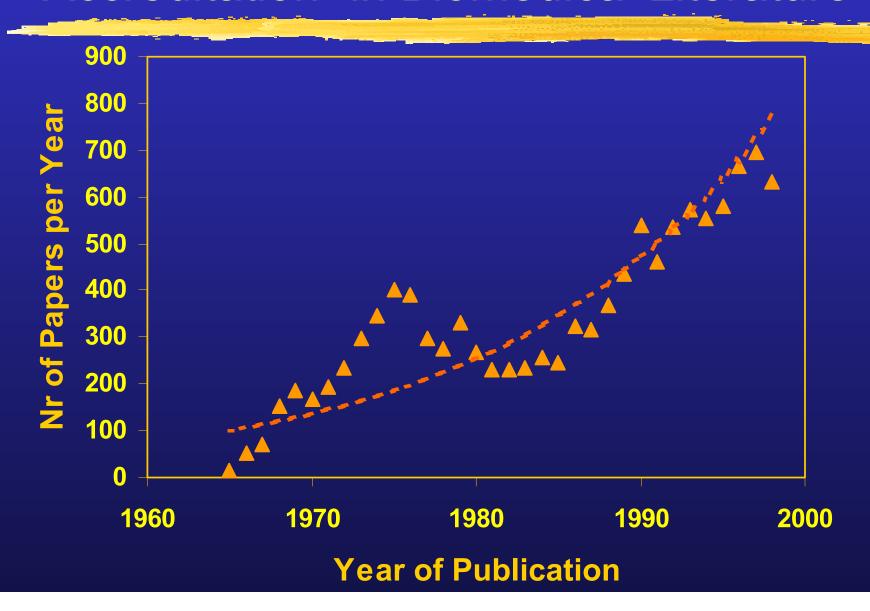
Reference Materials

PT is an important part of the "Check" in the Circle of Quality





"Accreditation" in Biomedical Literature



Within the last few months papers have appeared on:

- Proficiency testing program on mitochondrial DNA of the GEP-ISFG
- •BCR reference materials for quality assurance in environmental analysis
- Organic contaminants in water
- Antimicrobial resistance: standardisation and harmonisation of laboratory methodologies
- European proficiency testing program for molecular detection and quantitation of hepatitis B virus DNA
- Forensic textile fiber
- Trace element analysis in hair

Within the last few months papers have appeared on:

- •Anti-tuberculosis drug resistance: results of the 1998/1999 proficiency testing in Italy.
- •Classical swine fever virus: a second ring test to evaluate RT-PCR detection methods
- Neonatal bilirubin testing practices: reports from 312 laboratories
- •A continuous quality control program for strict sperm morphology
- Immunophenotyping in clinical flow cytometry
- Proficiency testing scheme for aromatic hydrocarbons in air
- Multicenter proficiency testing of nucleic acid amplification methods for the detection of enteroviruses

Within the last few months papers have appeared on:

- Laboratory performance assessment criteria in national asbestos fibre counting schemes
- Proficiency testing for laboratories involved in cadaveric organ transplantation
- Proficiency testing event for acid-fast microscopy
- •Extractable trace element contents of soil samples prepared for proficiency testing
- Proficiency testing in dairy laboratories.
- Aflatoxin M1 in milk
- Emerging antimicrobial resistance

How to assess laboratory quality?

If Proficiency Testing (External Quality Assessment) monitors actual performance, it could be the single most important quality indicator and an efficient manner to monitor the entire system.

The product of the laboratory (the analytical result) is evaluated.

Substantial difference in samples

A Proficiency Sample

- Usually identified
- Enter process at later stage
- Matrix Effects
- Extraordinary Reporting

A Patient Sample

- Anonymous (one of many)
- Enter process at earliest stage
- Drug Metabolite Effects
- Routine Reporting (Electronic)

Patient vs. Proficiency Testing

- Ordered by Physician or Health Provider
- Sample Obtained from Individual
- Sample Transport
- Accession
- Analysis
- Calculation of Results
- Reporting Results
- Result used for Patient Care

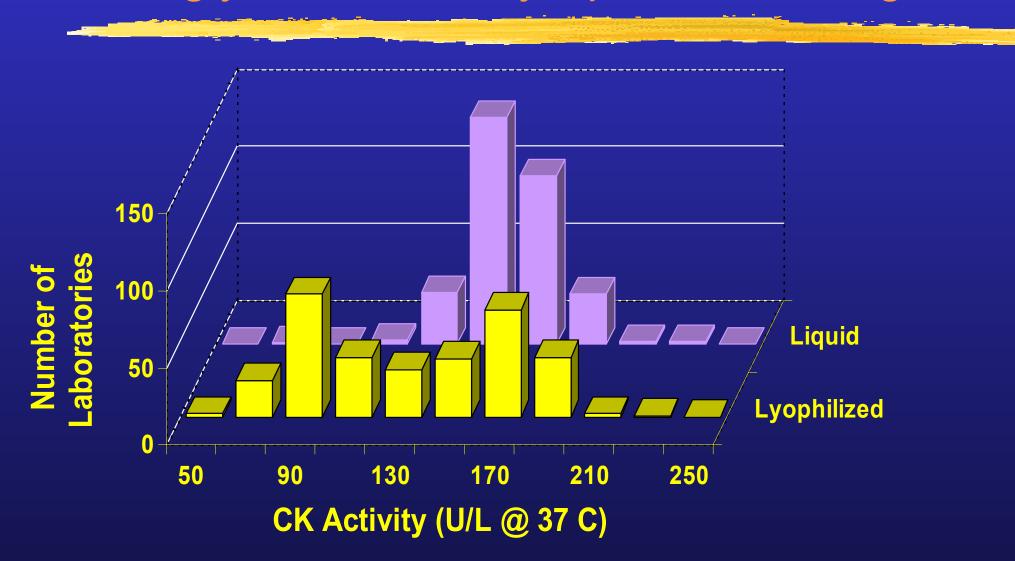
- Ordered by PT Provider, Client
- Sample Obtained from Large Pool
- Sample Transport
- Accession
- Analysis
- Calculation of Results
- Reporting Results
- Result used for Lab Evaluation

"... but we only have problems with your PT materials!"



- Lyophilization
- Additives
- Non-human source
- Method unspecificity

Estimates of Interlaboratory Dispersion May be Strongly Influenced by Specimen Design



Major Problems and <mark>Their Countermeasures</mark> on JMA/EQA Survey Materials (*from Kawai 2002*)

- Precision of lyophilization
 - Denaturation and volume of the content for each vial
 - Computer screening of all labs' results in a pre-set program by comparing among [Glu, ALT, CK] vs [Ca, IP, Fe] results for each lab
- Additives and denatuation during lyophilization
 - Free glycerol for triglyceride
 - p-Hydoxy benzoic acid for cholinesterase (with a reagent kit)
 - Poor separation during electrophoresis
 - Denaturation of lipoproteins
- Isoenzymes of animal origin
 - Recombinant human enzymes since 1990
- Unexpected matrix effects for selected assay systems

"Matrix-Effect" Errors with Patient Specimens?

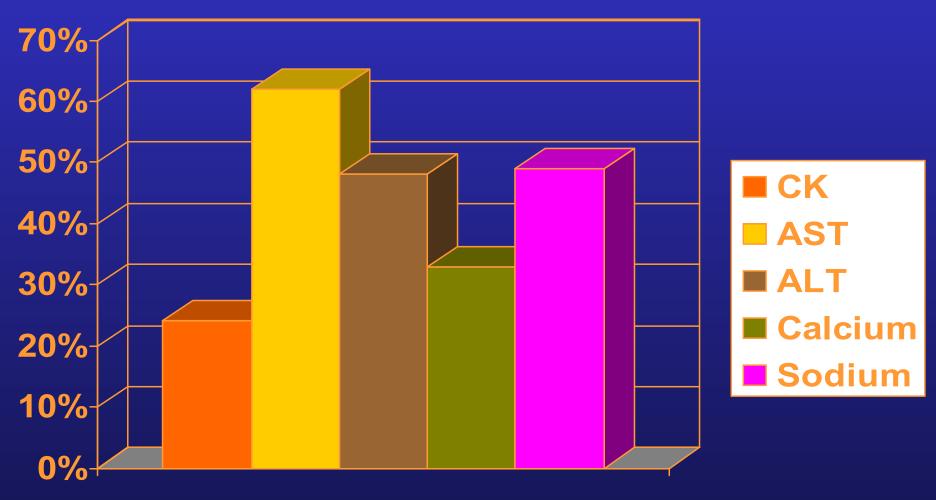
Differences in Specificity or Bias Between Two Laboratories.

Bias Between Two Methods within One Laboratory.

Specificity Differences Between Two Methods within One Laboratory.

Inappropriate Conversion Factors amongst Methods for Some Samples.

Patient Specimens with Unacceptable Intermethod Bias



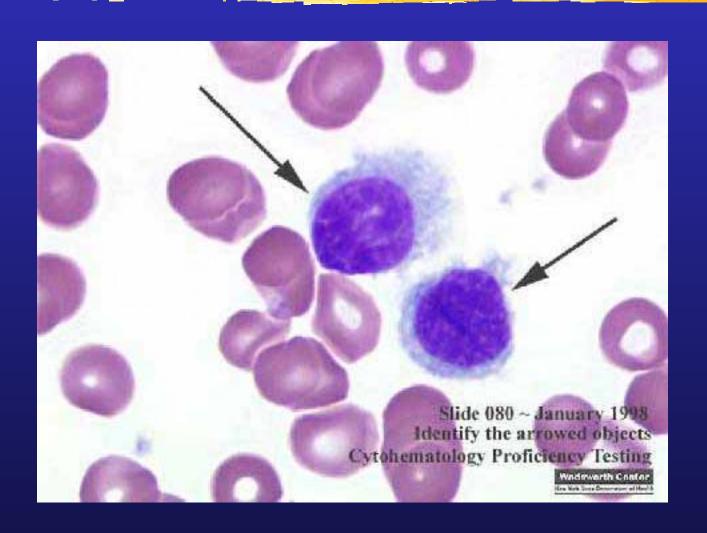
Unacceptable Bias for Monitoring (%)

Data from J.Kropf et al. Practical implications of coexistent technologies in clinical chemical laboratories. Eur J Clin Chem Clin Biochem. 29: 675 (1991)

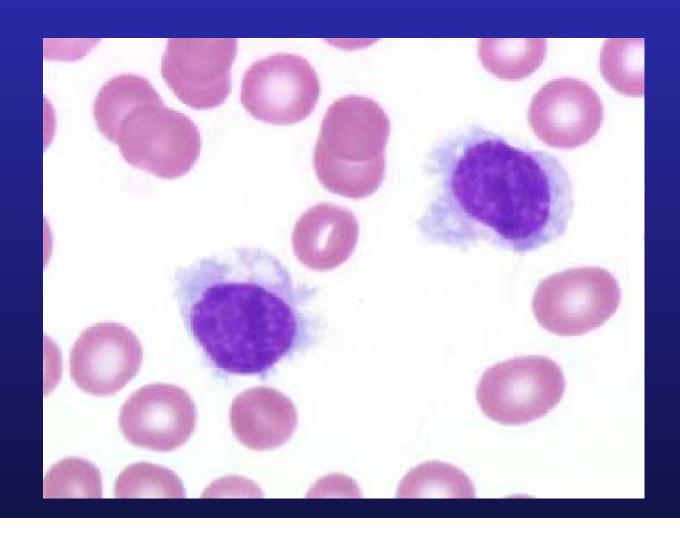
"Matrix effects" in Hematology Morphology

- Factors other than the analyte itself that effect the measured results
- Often considered to be an "artifact" where QC samples do not behave like patient specimens
- Cell identification from images (35mm slides or WWW) differ considerably from patient samples

35-mm slide: Hairy cell leukemia



Glass slide: Hairy cell leukemia



Difference in morphology error rates: 35-mm images *vs.* glass slides

	Errors 35mm	Errors Glass
Sickle cell	32 (7%)	3 (0.6%)
Howell-Jolly Body	3 (0.6)	105 (22%)
Spherocytes	9 (2%)	184 (39%)
Hairy cell	16 (4%)	14 (3%)

From Rej et al, NYS Dept Health

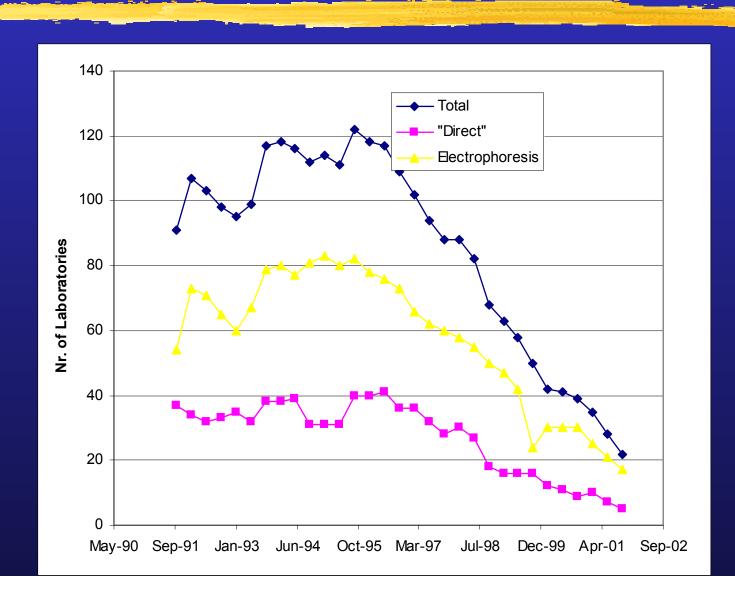
PT Provides Information on Laboratory Infrastructure & Trends

CREATINE KINASE ISOENZYMES

	1992	1995	2001
Immunochemical mass:	28%	50%	80%
Immunochemical activity	38%	31%	17%
Chromatography	10%	4%	0%
Electrophoresis	24%	15%	3%

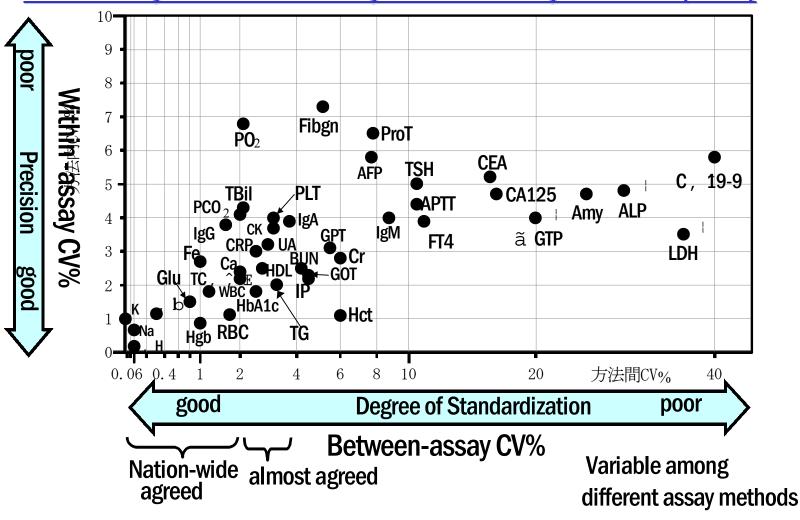
% = Percentage of laboratories using specified technique

Trend in use of LD Isoenzymes



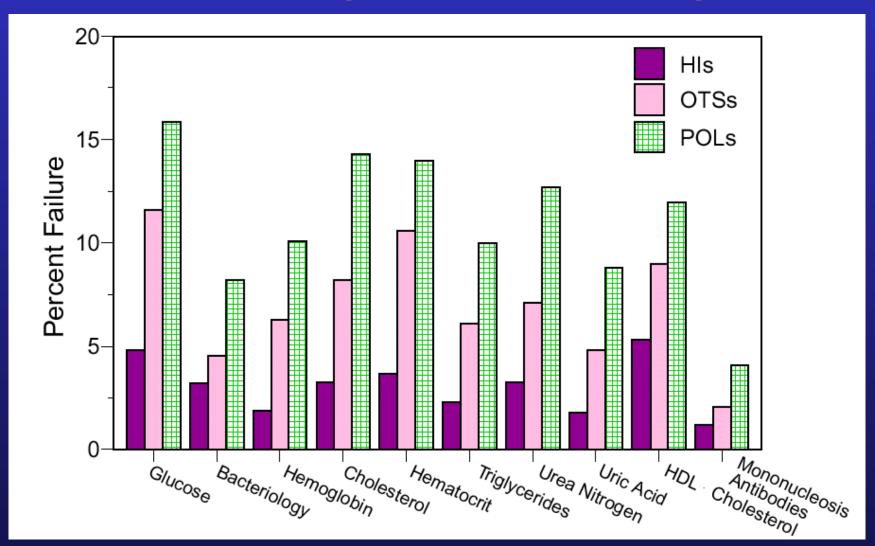
Priorities for Improvement

Within-Assay and Between-Assay Inter-Laboratory Variations (1999)



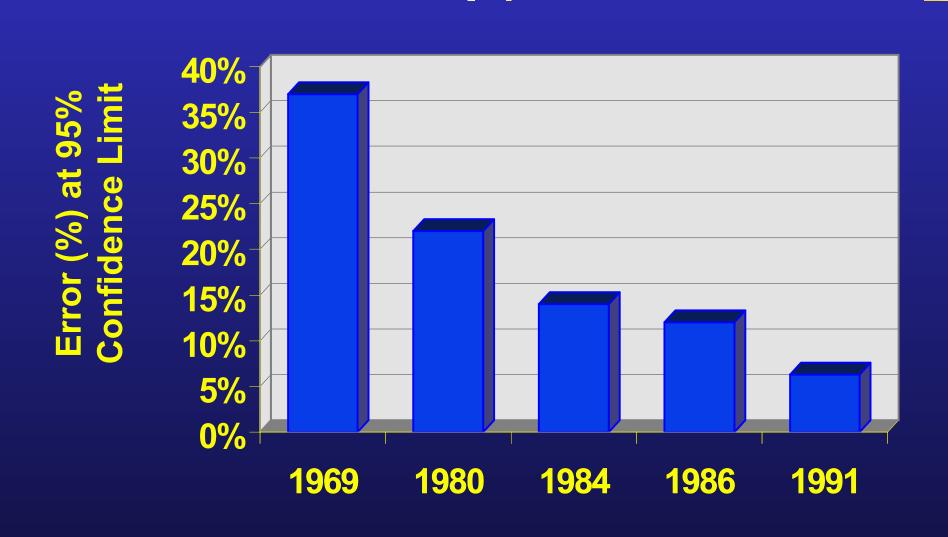
From Kawai (2002)

Proficiency Testing Failures in the US: 1994 (1.2 M Results)



From: MMWR 45: 193 (1996)

Interlaboratory Error for Cholesterol Measurements: 1969-1990



Issuing Reports

Paper,
paper,
paper...



UK NEQAS: Method-related data The early years (*circa 1975*)

OTAL ROTEIN		AutoAnalyser I Biuret	AutoAnalyser II or SMA system Biuret	Manual Biuret	Refractometer	Specific Gravity	Others
	No. of Values	115	<i>73</i>	102	10	2	12
	Mean	5.87	5.94	5.88	6.04	5:75	5:73
	S.D.	0.21	0.15	0.28	0.23	0.35	0.13
	CofV	3.7/	2.67	4-80	3.8	6.14	2.24

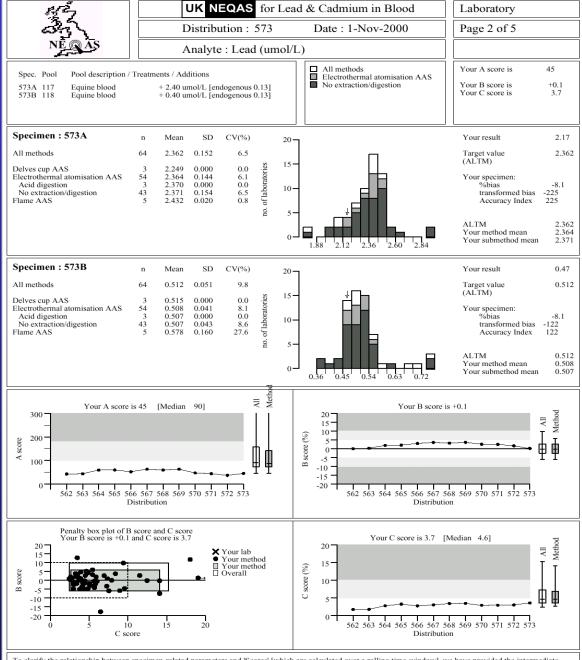
ALBUMIN

	AutoAnalyser I BCG	AutoAnalyser II or SMA system BCG	AutoAnalyser I HABA	AutoAnalyser II or SMA system HABA	Manual BCG	Manual Salt Fractionation and Biuret	Electrophoresis- Scanning and Elution
No. of Values	101	61		1	69	26	24
Mean	3.60	3.51		3.70	3.62	3.73.	3.59
s.D.	0.23	0.20		0.00	0.22	0.31	0.42
C of V	639	5.71		0.03	6.21	8.40	11.92

RESULTS ACCORDING TO METHODS IN USE

(Excluding those outside 3 v S n)

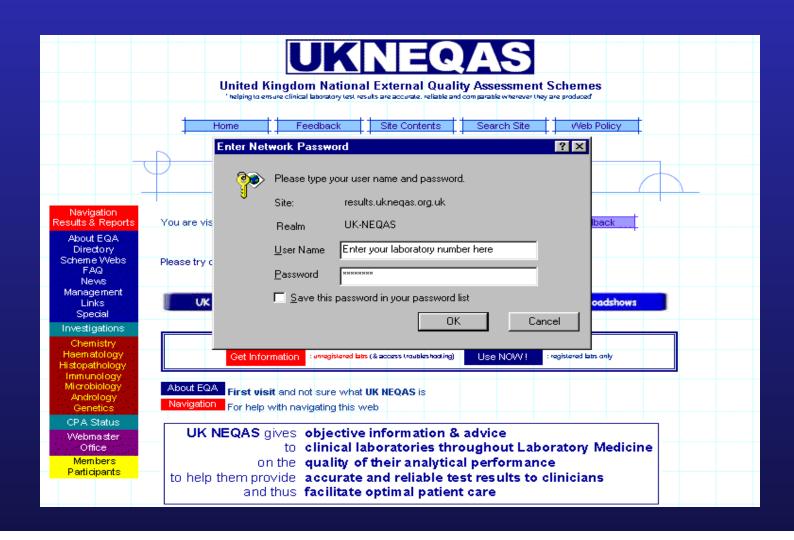




To clarify the relationship between specimen-related parameters and 'Scores' [which are calculated over a rolling time-window], we have provided the intermediate specimen %bias, specimen transformed bias and specimen Accuracy Indices used in the calculation of the A score.

UK NEQAS, Wolfson EQA Laboratory, PO Box 3909, BIRMINGHAM B15 2UE, UK Phone (direct) 0121-414 7300; FAX 0121-414 1179 © The data in UK NEQAS reports are confidential. This scheme is fully CPA(EQA) Accredited. www.ukneqas.org.uk email: queries@ukneqas.org.uk

Web-Based Secure Service



★ Return to the list of chemistry testing events

February 2001



Select an analyte:

Glucose

Urea Nitrogen

Creatinine

Uric Acid

Bilirubin

Phosphorus

Calcium

Magnesium

Iron

Sodium

Potassium

Chloride

Albumin

Total Protein

Cholesterol (Total)

HDL-Cholesterol

LDL-Cholesterol

Triglycerides

Homocysteine

Alanine Aminotransferase

Aspartate Aminotransferase

alpha-Amylase **Alkaline Phosphatase** gamma-Glutamyltransferase



New York State Department of Health - Wadsworth Center

Clinical Chemistry Proficiency Testing - February 12, 2001

Summary of Participant Performance (Mean and Standard Deviation)

Glucose (mg/dL)

Specimen		Specimen: C97	Specimen: C98	Specimen: C99	Specimen: COO	Number		Instrument or Reagent System
88.2 ±	3.09	187.8 ± 4.95	46.7 ± 2.32	102.9 ± 2.93	233.2 ± 7.23	n = 435	[]	All Methods & Instruments
85.9 ±	5.22	181.1 ± 8.31	47.9 ± 2.05	101.5 ± 5.43	225.8 ± 8.70	n = 3	[ABS]	Abbott Spectrum
86.2 ±	1.00	188.4 ± 1.52	45.4 ± 0.87	101.6 ± 0.94	236.9 ± 4.95	n = 8	[ABR]	Abbott Aeroset
86.5 ±	2.10	186.1 ± 3.20	45.1 ± 1.80	102.8 ± 2.23	229.4 ± 4.00	n = 97	[BCS]	Beckman Coulter SYNCHRON Systems
85.5 ±	1.47	178.0 ± 3.08	46.8 ± 1.96	98.6 ± 0.83	218.8 ± 6.31	n = 8	[COR]	Chiron Express
96.8 ±	4.33	211.1 ± 14.85	50.0 ± 0.00	109.5 ± 3.90	260.4 ± 17.70	n - 4	[CEA]	Cholestech LDX
88.2 ±	2.16	185.3 ± 3.18	47.6 ± 2.13	102.0 ± 2.35	229.2 ± 4.41	n = 62	[DUD]	Dade Behring Dimension
102.3 ±		191.9 ± 6.08	58.4 ± 2.56	116.4 ± 2.56	228.3 ± 5.86	n - 3	[HEA]	HemoCue
90.1 ±		191.9 ± 6.66	47.7 ± 2.21	105.8 ± 2.50	238.9 ± 4.86	n - 7	[HIC]	Hitachi 717
87.1 ±		188.0 ± 2.72	46.4 ± 1.15	103.7 ± 1.88	232.2 ± 3.49	n = 28	[HIF]	Hitachi 747
88.9 ±		192.4 ± 2.28	46.9 ± 0.86	106.3 ± 1.22	239.9 ± 1.92	n - 10	[HIG]	Hitachi 911
87.5 ±		189.1 ± 3.78	46.6 ± 0.75	104.4 ± 2.23	235.0 ± 6.09	n = 10	[HIJ]	Hitachi 917
87.3 ±		186.4 ± 3.67	45.9 ± 1.27	103.2 ± 2.23	230.4 ± 3.86	n = 9	[HIM]	Hitachi MODULAR
88.9 ±		191.8 ± 8.14	45.9 ± 1.38	107.1 ± 4.68	241.9 ± 10.74	n - 5	[IAA]	i-STAT
90.4 ±		190.2 ± 3.84	47.8 ± 2.08	102.1 ± 2.47	238.6 ± 4.88	n = 97	[JJE]	Johnson & Johnson Vitros
84.0 ±		183.1 ± 3.79	44.7 = 0.61	101.4 ± 1.77	226.8 ± 3.66	n = 12	[OLC]	Olympus AU 400/600/640
86.2 ±		183.3 ± 7.58	46.0 ± 3.61	101.5 ± 3.63	227.6 ± 9.68	n = 3	[OLA]	Olympus AU 800/1000
90.1 ±		189.3 ± 3.24	48.8 ± 0.83	104.9 ± 1.57	234.3 ± 4.71	n = 13	[OLB]	Olympus AU 5000/5200
85.9 ±		187.4 ± 2.76	45.3 ± 0.80	103.0 ± 2.17	234.8 ± 2.94	n = 9	[ROT]	Roche Cobas INTEGRA
87.5 ±		187.3 ± 10.50	45.4 ± 2.58	103.7 ± 5.50	234.9 ± 15.63	n = 14	[ROM]	Roche Cobas MIRA
85.6 ±		182.6 ± 2.54	43.8 ± 3.50	100.6 ± 2.05	227.7 ± 5.92	n = 6	[TNF]	Technicon DAX
90.2 ±	2.36	190.0 ± 2.70	48.0 ± 1.80	104.5 ± 1.86	237.5 ± 2.74	n = 3	[TNZ]	Technicon, other
86.6 ±	2.79	187.3 ± 5.72	45.7 ± 1.51	101.7 ± 0.87	234.7 ± 8.12	n = 10	[AB1]	Abbott
86.5 ±	2.28	186.2 ± 3.37	45.1 ± 1.85	102.9 ± 2.35	229.4 ± 4.07	n = 96	[BC1]	Beckman Coulter
96.8 ±	4.33	211.1 ± 14.85	50.0 ± 0.00	109.5 ± 3.90	260.4 ± 17.70	n - 4	[CE1]	Cholestech
85.1 ±	1.40	177.4 ± 3.05	46.0 ± 1.21	98.5 ± 0.71	217.5 ± 4.36	n = 8	[CO1]	Chiron
88.3 ±	2.26	185.5 ± 3.47	47.7 ± 2.19	102.0 ± 2.44	229.4 ± 4.68	n = 64	[DA1]	Dade Behring
91.2 ±		191.2 ± 8.77	50.2 ± 2.36	106.1 ± 5.22	239.8 ± 12.13	n = 3	(EL1)	Elan Diagnostics
102.3 ±		191.9 ± 6.08	58.4 ± 2.56	116.4 ± 2.56	228.3 ± 5.86	n = 3	[HE1]	HemoCue
86.0 ±		186.2 ± 1.54	44.8 ± 2.36	102.6 ± 1.02	231.9 ± 3.72	n - 3	[HC1]	HiChem
88.1 ±		189.6 ± 7.44	45.8 ± 1.54	106.5 ± 4.61	239.0 ± 10.00	n = 3	[IA1]	1-STAT 37C cartridges
90.5 ±		190.3 ± 3.87	47.8 ± 2.10	102.2 ± 2.51	238.7 ± 4.97	n = 99	[331]	Johnson & Johnson
87.2 ±		186.3 ± 5.32	46.7 ± 2.53	103.1 ± 2.75	230.6 ± 6.46	n = 27	[OL1]	Olympus
86.8 ±		187.9 ± 7.77	45.3 ± 1.94	103.3 ± 4.46	236.3 ± 10.66	n = 22	[RO1]	Roche
87.6 ±		189.2 ± 3.91	46.4 ± 1.19	104.3 ± 2.31	234.3 ± 5.27	n = 63	[ROZ]	Roche/Hitachi
90.8 ±		190.7 ± 7.41	48.8 ± 2.31	105.9 ± 2.63	233.6 ± 7.77	n = 03	[SI1]	Signa.
87.5 ±	4.87	185.2 ± 4.87	46.0 ± 3.99	102.2 ± 3.59	232.6 ± 8.97	n = 10	[TN1]	Technicon

Distribution: Another common problem

Labor intensive

Shippers' rules

Packaging requirements

Variable time-frames

Customs delays

Irradiation



Assessing Lab Quality via PT?

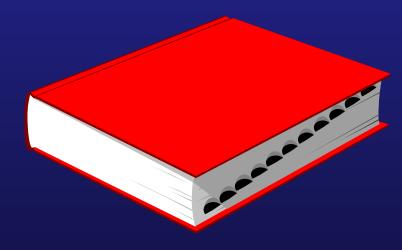


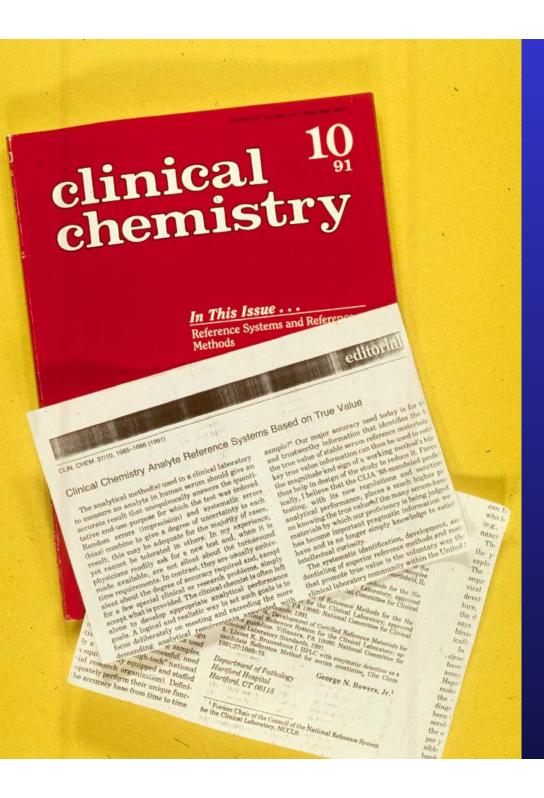
good ('gûd), adj.;

9. Of comparative excellence in its kind; approaching the standard; commendable.

good ('gûd), adj.;

13. Biol. = TRUE





Bowers GN Jr Clin Chem 37:1665 (1991)

Schoen I CAP Today 6 (7):80 (1992)

Tietz NW Clin Chem 38:473 (1992) Clin Chem 40:859 (1994)

TRACEABILITY SHOULD BE AN IMPORTANT COMPONENT OF PT

The ability to relate to individual measurement results to national or international standards through an unbroken chain of comparison.

B.C. Belanger, Traceability - An Evolving Concept. ASTM Stand. News <u>8:</u> 22 (1980).



ESTING — Melinda Falzo, a medical technician at Bender Labs, necks blood to be put into a machine which tests for cholesterol.

Results vary widely a cholesterol tests

Stephen Frank

writer

he results of routine blood tests for cholesterol vary so much from one laboratory to another that the numbers seriously mislead patients about r coronary health.

he confusion — at a time of the heart disease — is like to heart disease — is sed by an inability to standardize scores carried diametrically opposite therapeutic implications.

The reporter's low result — 119 mg/dl — signified little increased risk of developing heart disease and would have been reassuring to most patients and to many physicians.

But the high result — 235 mg/dl — carried significant risk. It was well above the threshold that triggers a physician's concern and at which dietary changes are recommended and

CHOLESTEROL LEVELS VARY DEPENDING ON TEST

Different cholesterol tests provide different results. Here is a comparisor of three common tests – the LRC, SMAC and the Du Pont aca.

DIFFERENT CHOLESTEROL TESTS							
	MOD	MODERATE RISK			HIGH RISK		
AGE	LRC	SMAC	C aca	LRC	SMAC	aca	
20-29	200	225	240	220	250	265	
30-39	220	250	265	240	275	290	
40+	240	275	290	260	295	315	

SOURCE: InfoGraphics, The Health Letter

Peer Grading:

- Obviates matrix effect
- No impact on patient
- A necessary evil
- A vicious circle

Original Intent of CLIA'88 was to Standardize Results amongst Laboratories

Target value for quantitative tests:

- 1. Mean of Participants
- 2. Definitive or Reference Method (NRSCL)

Exceptions (Peer-group Evaluated):

- 1. No Reference Method Available
- 2. Biases not Observed with Patient Samples



Peer Grading?

Johannes Büttner:

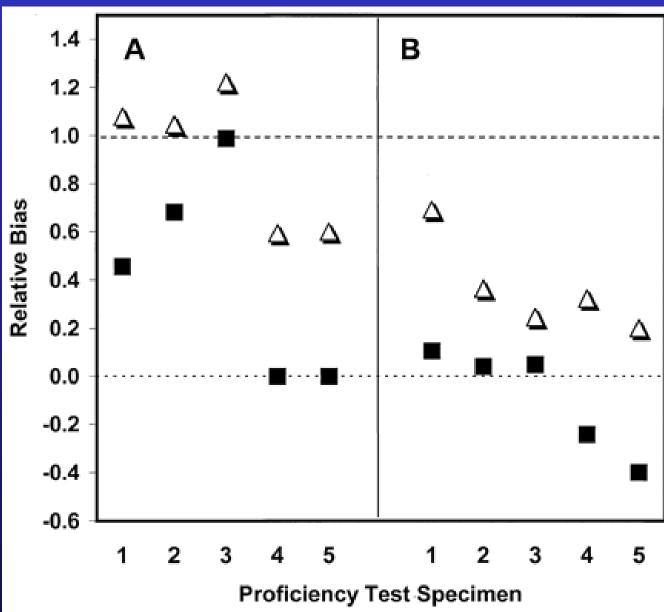
".. in the proficiency testing, so called 'peer group mean values' are employed as target values, and these do not lead to any improvement of the trueness or therefore of the comparability."

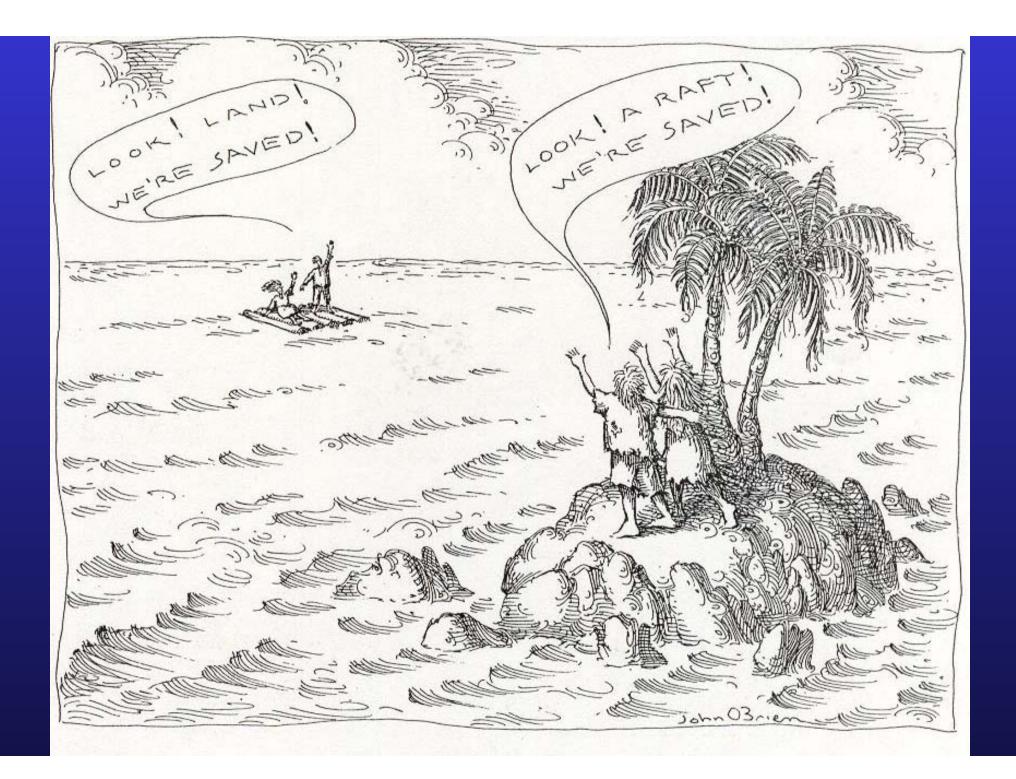
Eur J Clin Chem Clin Biochem 1995;33:981-88

"Peer grading" can mask true errors

 \blacksquare = Peer \triangle = Overall

Thyrotropin
From Rej et al, Clin Chem



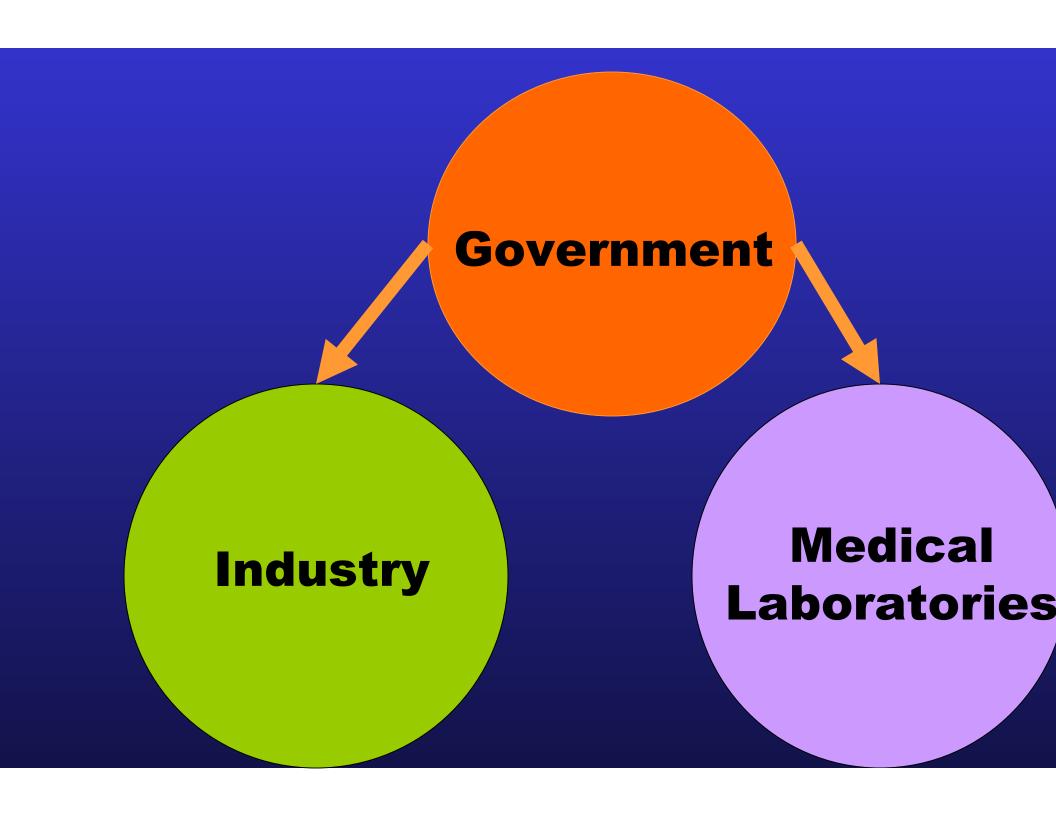


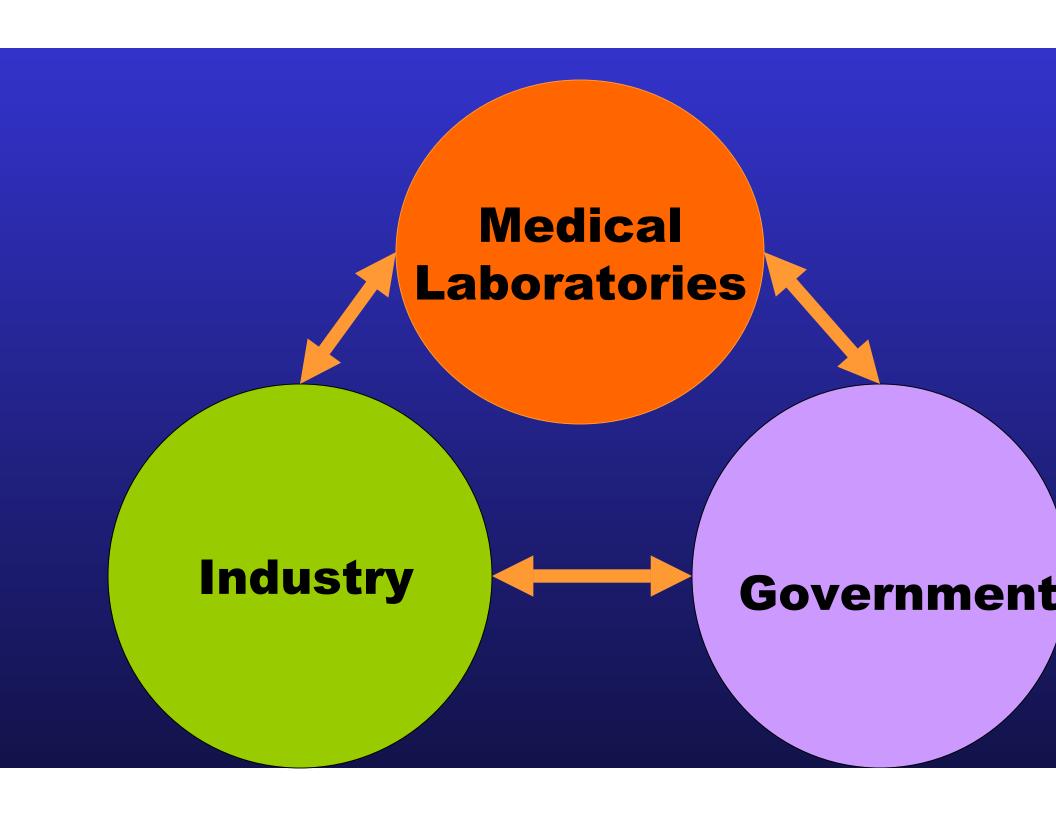
Using PT in Regulatory Programs

"Using proficiency testing for law enforcement is like using a chisel to drive a screw. You can do it, but it doesn't work very well and it dulls the tool for the jobs it can do better." (DB Dorsey)

Regulatory Proficiency Testing: The Problems of Pass/Fail

- Event 1: + + + - Fail
- Event 2: + + + + Pass
- Event 3: + + + - Fail
- 4 incorrect analyses (27%) = Unsuccessful
- Event 1: Fail
- Event 2: + + + Pass
- Event 3: + + + + Pass
- 7 incorrect analyses (47%) = Successful





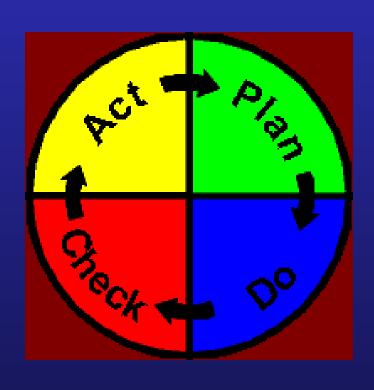


"My question is: Are we making an impact?"

Does Proficiency Testing Improve Laboratory Performance?

- Passing PT provides evidence of meeting practice standards (national or survey).
- The efforts expended are expected to result in improved performance.
- Difficulties lie in estimating performance of laboratories that lack PT assessment (what are indicators of performance?).
- Concurrent improvements in technology with increased PT activity

PT is an important part of the "Check" in the Circle of Quality





Do Proficiency Testing Participants Learn From Their Mistakes?

Participants: a large PT program (EXCEL), designed for clinic and office laboratories

Specific competence: the ability to differentiate group A streptococcus from group C streptococci

Time frame: a 6-year period (1996 - 2001)

Results: Despite consistent feedback, there was no significant change in participant performance throughout the period studied.

Conclusions: current utilization of proficiency testing results in laboratory improvement programs is suboptimal.

Novak RW: Arch Pathol Lab Med 2002 Feb;126(2):147-149

Reasons for poor performance in PT

Factor	Percent
Poorly trained laboratory analysts	86%
Inadequate number of laboratory analysts	84%
Lack of understanding between directors and laboratory analysts	67%

Many facets of Proficiency Testing

Traceability

Legal Authority

Education

Snapshot of Performance

Measurement Uncertainty

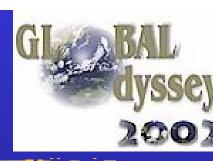
National Infrastructure

Accreditation

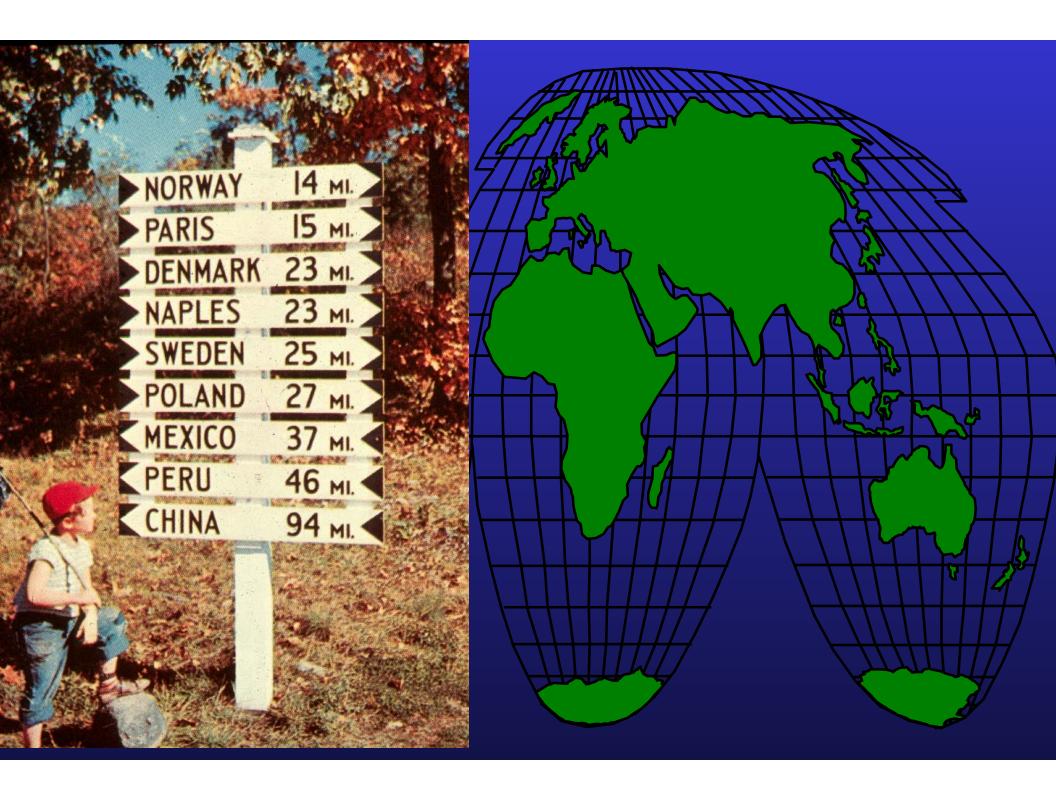
International Measurement Structure

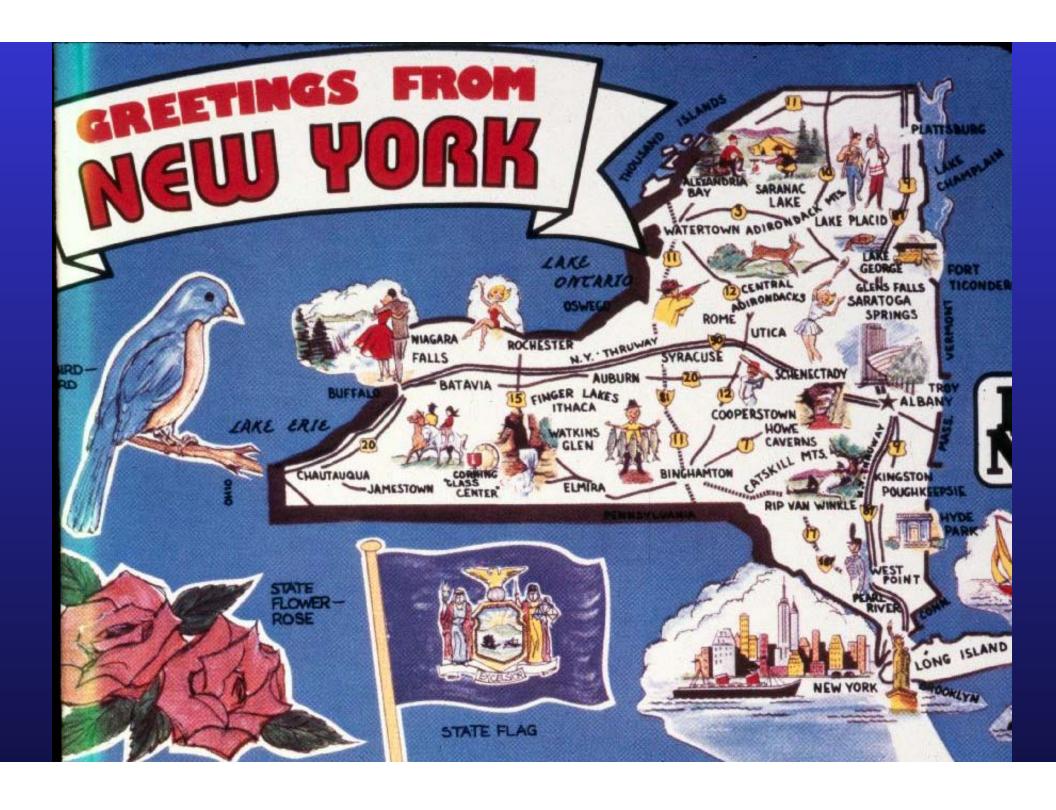
Reference Materials

Expectations and Outcomes



- Provide a forum for all interested parties
- Opportunity to learn from the successes (and failures) of others
- "Twinning" of resource diverse programs or interests
- New advances in scope, mechanics, and interpretation of PT
- Optimize educational and outcomes aspects, particularly by Internet applications
- Starts not ends on 26 February 2002





Thank you for your attention!

